## REMARKS

Claims 1-13, 17, 21 and 22 are pending, claims 15-16 having been cancelled. New claim 21 was added. No new matter has been added by this amendment.

***Claim Rejections--35 U.S.C.§ 103***

Claims 1-7, 12, 13, 15-17, 20, and 21 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Harrington et al., Spine 25(9):929-36 (2000) ("Harrington") in view of Slivka et al (US 2003/0181365; "Slivka") in further view of Lawand, et al., Euro J of Pharmacology 324:169-77 (1997) ("Lawand").

Claim 1 and claims that are dependent upon claim 1 are drawn to a method of alleviating pain in a mammal by contacting a neuronal cell of a cartilaginous tissue with an antagonist of a glutamate receptor directly into herniated disc tissue such that inhibition of binding of free glutamate liberated from the degenerating cartilage to the glutamate receptor alleviates pain. Claims 15 and 16 have been canceled. Claims17, 20, and 21 require an articulating joint tissue such as an elbow or knee.

The Examiner relies on one of the "Key Points" on page 935 of Harrington, which states, "Enzymatically degraded herniated disc material could be a source of free glutamate that would potentiate pain signals by acting on glutamate receptors on the dorsal root ganglion neurons." This reference suggests the possibility that local injections, i.e., delivery to the epidural space, of glutamate receptor antagonists may be beneficial in treatment of pain. This suggestion, however, is predicated on the prerequisite that "free glutamate from disc material arriving at the DRG affects nociception" (p. 935, top of column 1). As stated by the authors in that same paragraph, at the time of publication, it was not yet know whether such an event occurs. As noted by the Examiner, this reference fails to describe or suggest direct administration to the disc itself.

Slivka describes delivery of a chemical crosslinker to an intervertebral disc for the purpose of crosslinking native molecular components rather than removing or dissolving them. The disclosure of injecting of one type of medicament directly into disc tissue does not suggest that injection of a completely different medicament would be obvious. A chemical crosslinking agent to crosslink and stabilize/stiffen the disc structure is fundamentally different from a glutamate receptor antagonist. The Slivka reference fails to describe or suggest the release of any free amino acids (much less glutamate) from disc material or any mediators of pain from disc

material. Therefore, one of skill in the art would not be inclined to combine these two references.

This obviousness rejection is further based on a tertiary reference - Lawand. Lawand. Lawand describes an experimental system in which a knee joint cavity of a rat was injected with L-glutamate (as well as other amino acids such as L-aspartate, L-arginine, and combinations thereof). Subsequent intra-articular injection of NMDA or non-NMDA receptor antagonists resulted in attenuation of thermal hyperalgesia or response to a painful stimulus. However, this reference simply concludes that there is "evidence for a potential role of peripheral NMDA and non-NMDA receptors in nociceptive transmission" rather than suggesting that excitatory amino acids are actually released by injured tissue, much less disc tissue (a tissue that is fundamentally different in anatomical location, biochemical composition, and physiological function from knee joint cavity tissue). There is no suggestion that glutamate is released from knee cartilage tissue, much less disc cartilage tissue.

Since none of the cited references describe or suggest the presence of glutamate receptors in herniated disc tissue, there is no motivation to combine these references. Without such a suggestion, one of skill in the art would have no reason whatsoever to administer a glutamate receptor antagonist directly into herniated disc tissue as required by the claims. Withdrawal of this rejection is respectfully requested.

Claims 1, 8, and 11 were rejected for obviousness over the same combination of references in further view of Stanfa et al., Neuroscience 93(4):1391-98 (1999) ("Stanfa"). The key elements of claim 1 were discussed above. Claim 8 requires certain specific KA receptor antagonists, and claim 11 requires certain specific metabotropic glutatmate receptor antagonists. Stanfa was relied upon to provide a description of the specific antagonists, but fails to provide any further rationale for combining Harrington, Slivka, and Lawand.

Claims 1, 9, and 10 were rejected for obviousness over Harrington, Slivka, and Lawand, in further view of Garrett (Biol. Res. for Nursing, Vol. 1 No.4, Apr 200). The latter of the references was apparently cited for disclosure of L-AP3. Garrett is a review article of metabotropic glutamate receptors and the perception of pain. There is nothing in Garrett to support the combination of the foregoing individual publications cited by the Examiner.

None of the cited references alone or in combination describes the foundation upon which claims are based, much less the very specific delivery route or anatomical locations required by

the claims. Without description of that foundation, there is not motivation to select the specific claimed routes of administration or anatomical locations, and the pending obviousness rejections fall short. Without a description or suggestion that glutamate receptors exist in disc tissue, there is no reason one of skill in the art would administer a glutamate receptor antagonist to that tissue. Without a description or suggestion that cartilaginous tissue of an articulating joint such as a knee or elbow is a depot/source for free glutamate, the skilled artisan would not be motivated to administer glutamate receptor antagonists to the joint space of such articulating joints.

Applicants submit that the amended claims are nonobvious in view of the art of record and requests the Examiner's reconsideration of the pending rejections.

## CONCLUSION

Applicant submits that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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